

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

Wipo

PCT

REC'D 18 MAY 2005

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:
OGILVY RENAULT
1600 - 1981 McGill College Avenue
MONTREAL, Quebec
Canada, H3A 2Y3

21/7

Date of mailing (day/month/year) 11 May 2005 (11-05-2005)

Applicant's or agent's file reference
8426-1851PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/CA2005/000007

International filing date (day/month/year)
06 January 2005 (06-01-2005)

Priority date (day/month/year)
08 January 2004 (08-01-2004)

International Patent Classification (IPC) or both national classification and IPC (IPC 7) C07D403/12, C07D405/12, C07D309/30, C07D211/74, C07D207/24, C07D213/65, C07D401/12, A61K31/341, A61K31/445, A61K31/44, A61K31/44, A61K31/40, A61K31/55, A61K31/4433, A61K31/506, A61P19/08

Applicant
MERCK FROSST CANADA & CO. ET AL

1. This opinion contains indications relating to the following items :

- | | |
|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input checked="" type="checkbox"/> Box No. I | Basis of the opinion |
| <input checked="" type="checkbox"/> Box No. II | Priority |
| <input type="checkbox"/> Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> Box No. V | Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement. |
| <input type="checkbox"/> Box No. VI | Certain documents cited |
| <input type="checkbox"/> Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9

Authorized officer

Gérald McManus (819) 956-6126

Facsimile No: 001(819)953-2476

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CA2005/000007

Box No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language which it was filed, unless otherwise indicated under this item.

[] This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :
 - a. type of material
 - [] a sequence listing
 - [] table(s) related to the sequence listing
 - b. format of material
 - [] in written format
 - [] in computer readable form
 - c. time of filing/furnishing
 - [] contained in the international application as filed.
 - [] filed together with the international application in computer readable form.
 - [] furnished subsequently to this Authority for the purposes of search.
3. [] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments :

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CA2005/000007

Box No. II

Priority

1. ☐ The following document has not yet been furnished :

☐ copy of the earlier application whose priority has been claimed (Rules 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rules 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary :

The validity of the priority has not been checked because the priority document was not available to the examiner for review. Therefore, the priority date was considered valid for the establishment of the Written Opinion.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. V **Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-12	YES
	Claims		NO
Inventive step (IS)	Claims	1-12	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations :

D1 = P. SAFTIG ET AL.: "IMPAIRED OSTEOCLASTIC BONE RESORPTION LEADS TO OSTEOPETROSIS IN CATHEPSIN K-DEFICIENT MICE"
PROG. NATL. ACAD. SCI. USA,
vol. 95, No. 23, November 1998, pages 1353-1358

D2 = S.K. THOMPSON ET AL.: "DESIGN OF POTENT AND SELECTIVE HUMAN CATHEPSIN K INHIBITORS THAT SPAN THE ACTIVE SITE"
PROG. NATL. ACAD. SCI. USA
vol. 94, No. 26, December 1997, pages 14249-1454.

Document D1 discloses the molecular processes underlying osteopetrosis in cathepsin-K-deficient mice which might serve in the evaluation of cathepsin-K inhibitors for therapeutic use. Document D2 discloses the design and synthesis of novel bis(aza)-1,3-diamino-2-propanones compounds that are potent and selective inhibitors of cathepsin-K. Said inhibitors have demonstrated antiresorptive activity both in vitro and in vivo and therefore are promising leads for therapeutic agents for the treatment of osteoporosis.

A. Novelty

The claimed invention relates to a novel class of compounds mainly, leucinamide-4-fluoroleucyl-amino-carboxylate derivatives. Said compounds are cathepsin cysteine protease inhibitors, including but not limited to, inhibitors of cathepsin K, L, S and B and to pharmaceutical compositions thereof. These compounds are useful for treating and preventing cathepsin dependent conditions in which inhibition of bone resorption is indicated, such as osteoporosis.

Claims 1-12 do meet the criteria under PCT Article 33(2) for novelty.

B. Inventive step

Claims 1-12 do meet the criteria under PCT Article 33(3) for inventive step.

C. Industrial applicability

Claims 1-12 do meet the criteria under PCT Article 33(4) for industrial applicability.

**WRITTEN OPINION OF THE
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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

The expression "incorporated by reference" on pages 1, 2, 17, 18, 19 and 27 is objected to under PCT Article 5.

The description is objected to under Article 5. The chemical formula described on page 44, line 3 is incorrect because it does not represent a leucinamide compound. The carbon atom linking the carbonyl of 4-bromophenyl-2,2,2-trifluoroethyl-4-fluoro-L-leucine to the 2-methyl-4-oxotetrahydrofuran-3-yl should be replaced with an amine group.

Claims 1, 3 and 5 are objected to under Article 6. The terms "aryl", "heteroaryl", "monocyclic", "bicyclic", "haloalkyl", "keto", "alkoxy" and "heterocyclyl" are open-ended and as such indefinite. The scope of these terms is impossible to determine. These terms are non-limitative and embrace an infinite number of possibilities not yet explored by the applicant. They therefore encompass possibilities, which are not regarded as obvious modifications of the examples given.

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